TRANSMITTAL LETTER OT THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Attorney Docket No. **2503-1008** U.S. Application No. **10/089728**

INTERNATIONAL APPLN. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/EP00/09750	**5 OCTOBER 2000**	**8 OCTOBER 1999**

TITLE OF INVENTION: **USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS**

APPLICANT(S) FOR DE/EO/US: **GIAN LUIGI GESSA, GIANCARLO COLOMBO, GIOVANNI ADDOLORATO**

Applicant herewith submits to the United States Designated Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau)
   b. ☐ has been communicated by the International Bureau. See attached PCT/IB/308.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☐ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☐ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ Information Disclosure Statement (IDS) w/PTO-1449 - ☒ Copy of IDS citations
12. ☐ Assignment Papers (cover sheet & document(s))
13. ☒ A FIRST Preliminary Amendment.
14. ☐ A SECOND or SUBSEQUENT Preliminary Amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule
18. ☐ A second copy of the published international application under 35 U S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application (35 U.S.C. 154(d)(4)).
20. ☒ Other items or information: **International Search Report, PCT/IPEA/409, Abstract of the Disclosure on a Separate Sheet, Application Data Sheet**

Y & T 2/12/02

JC13 Rec'd PCT/PTO 0 4 APR 2002

U.S. APPLICATION NO. 10/089728	INTERNATIONAL APPLN NO. PCT/EP00/09750	ATTORNEY DOCKET NO. 2503-1008

21. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1)-(5):		
Neither international preliminary examination fee nor international search fee paid to USPTO and international Search Report not prepared by the EPO or JPO $1040.00		
International preliminary examination fee not paid to USPTO but International Search Report prepared by the EPO or JPO $890.00		
International preliminary examination fee not paid to USPTO but International search fee paid to USPTO $740.00		
International preliminary examination fee paid to USPTO but all claims did not satisfy provision of PCT Article 33 (1)-(4) $710.00		
International preliminary examination fee paid to USPTO and all claims satisfied provision of PCT Article 33 (1)-(4) $100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT	$ 890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☐ 20- ☒ 30 months from the earliest claimed priority date (37 CFR 1.492(e))	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	2 - 20 =	0	X $18.00	$	
Independent Claims	2 - 3 =	0	X $84.00	$	
MULTIPLE DEPEND CLAIM(S) (if applicable)			+ $280.00	$	
			TOTAL OF ABOVE CALCULATION -	$ **1,020.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½ +				$	
			SUBTOTAL =	$ 1,020.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492Z(f)).				$	
			TOTAL NATIONAL FEE =	$ 1,020.00	
Fee for recording the enclosed assigned (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property +				$	
			TOTAL FEES ENCLOSED -	$ 1,020.00	
				Amount to be refunded	$
				Charged:	$

☒ A Check in the amount of **$1,020.00** to cover all fees is attached.

☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to Deposit account No. 25-0120 in the name of Young & Thompson, as described below. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17.

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PATENT TRADEMARK OFFICE

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Date: **April 4, 2002**

Benoit Castel
SIGNATURE

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35,041
REGISTRATION NO.

Y & T 2/12/02

PATENT
2503-1008

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of: Gian Luigi GESSA et al.

Appl. No.: **NEW** Group:

Filed: April 4, 2002 Examiner:

For: USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

April 4, 2002

Sir:

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

IN THE CLAIMS:

Please cancel claims 1-2 without prejudice or disclaimer of the subject matter contained therein.

Please add the following claims:

--3. (new) The use of baclofen or any stereoisomer thereof for the preparation of a medicament for the treatment of alcoholism in humans.--

--4. (new) Pharmaceutical compositions for the treatment of alcohol addiction and withdrawal syndrome, containing baclofen or any stereoisomer thereof as the active principle.--

REMARKS

Claims 3-4 are pending in the present application. Claims 1-2 have been cancelled and claims 3-4 have been added.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

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Attachments

ABSTRACT OF THE DISCLOSURE

The use of baclofen for the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

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THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS

The present invention relates to the use of Baclofen in the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

TECHNOLOGICAL BACKGROUND

Alcoholism is a serious medical, social and economic problem facing almost all human societies worldwide. Alcoholism has been diagnosed in an estimated 5% of adult population in the Western countries, while a larger number of people have been classified as problem drinkers (i.e. people who drink alcohol at a level that is risky for their health). Medical interventions in the field of alcoholism are primarily aimed at a) relieving the consequences of alcohol withdrawal syndrome and b) arresting alcohol drinking, maintaining sobriety for as long as possible. Pharmacotherapy is conceived to provide a substantial contribution to these goals, facilitating the psychological support and social rehabilitation of alcoholic patients.

Several pharmacological substances acting on neurotransmitter systems affected by the action of alcohol have been studied, naltrexone (Volpicelli et al., 1992; O' Malley et al., 1992), acamprosate (Withworth et al, 1996), fluoxetine (Naranjo et al, 1994), may be mentioned, inter alia. Furthermore, gamma-hydroxybutyric acid (GHB) a compound with behavioral GABA-like effects (Colombo et al., 1998), proved able to decrease alcohol intake in rats (Agabio et al., 1998) and humans (Gallimberti et al., 1992) and to induce alcohol abstinence in alcoholics (Addolorato et al., 1996; 1998a; 1998b). In addition, GHB proved to be effective in treating alcohol withdrawal syndrome both in

experimental animals (Gessa et al., 2000) and humans (Gallimberti et al., 1989), with a similar efficacy to diazepam (Addolorato et al., 1999b). It has been hypothesized that the effects of GHB on alcohol intake, craving and withdrawal syndrome are related to its alcohol-mimicking effect on the CNS (Colombo et al., 1995).

Baclofen, (beta-(4-chlorophenyl)-gamma-aminobutyric acid), a lipophilic derivative of GABA, is a potent and stereoselective $GABA_B$ receptor agonist. At present it is used clinically to control spasticity (Davidoff, 1985).

Baclofen has already been tested in experimental animals to evaluate its capacity to induce a selective reduction of daily alcohol intake in Long Evans rats (Daoust et al., 1987); on the other hand, subsequent studies reported that a higher dose of baclofen stimulated daily alcohol intake during both acquisition (Smith et al., 1992) and maintenance (Smith et al., 1999) phases of alcohol drinking behaviour in Long Evans rats; finally, central administration of baclofen failed to alter alcohol intake in Wistar rats (Tomkins and Fletcher, 1996). With regard to alcohol withdrawal syndrome, File and colleagues (1991) reported that small doses of baclofen reduced the anxiety-like behaviours and tremors associated with alcohol withdrawal syndrome in alcohol-dependent rats; however, no effects on alcohol withdrawal tremors after baclofen administration were observed in mice (Humeniuk et al., 1994) and rhesus monkeys (Tarika and Winger, 1980).

Therefore, it was not possible to envisage a therapeutic effect of baclofen in the treatment of alcoholism on the basis of the aforementioned studies.

DISCLOSURE OF THE INVENTION

Based on the clinical evidence available and on results obtained with reliable experimental models, it has

been observed that baclofen may be successfully used in the treatment of alcoholism.

In the present invention, "baclofen" is intended as all baclofen stereoisomers as well as the mixtures thereof.

The results obtained by means of the present invention allow the overcoming of uncertainties as to inconsistencies and discrepancies in the above data which, when considered as a whole, made baclofen appear unsuitable for the specific aims.

Baclofen activity has been evidentiated in both a clinical study, as well as in Wistar rats previously rendered physically dependent on alcohol by the repeated administration of intoxicating doses of alcohol. Similar findings have been obtained using *Sardinian alcohol-preferring* (sP) rats, which are a predictive, reliable experimental model.

Accordingly, baclofen will be administered to alcoholic patients at daily dosages ranging from 10 to 50 mg, preferably from 15 to 30 mg, using conventional pharmaceutical compositions, preferably pharmaceutical compositions suited to oral administration.

The drug will be administered once or more times daily, and may be protracted for several weeks (for example, 3 to 6 weeks or more), in view of the fact that baclofen is well tolerated, is not toxic and does not induce addiction phenomena.

The invention will be now described in greater detail in the following Examples.

Example 1: Effect of baclofen on alcohol withdrawal syndrome

Animals

Male Wistar rats (Charles River, Calco, CO, Italy), weighing 275-300 g were used. After delivery, rats were

left undisturbed for 7 days to acclimatize to new housing conditions. Animals were housed 5 per cage with wood chip bedding under an artificial light-dark cycle of 12/12 hr (light on at 7:00 hr), at a constant temperature of 22±2°C and relative humidity of 60%. Rats were given free access to water and standard laboratory food (MIL Morini, San Polo d'Enza, RE, Italy) throughout the entire experiment.

Intoxication procedure

Rats were rendered physically dependent on alcohol by the method of Majchrowicz (1975). This consisted of 4 daily administrations of alcohol solution (20% w/v, in tap water) by intragastric gavage for 6 consecutive days, in order to maintain constant blood alcohol concentrations. Alcohol was administered at 6:00, 12:00, 18:00 and 24:00 hr. At the initial administration of the treatment, 4 g/kg alcohol were given to all rats. The assessment of subsequent doses was determined individually for each rat at the above administration times on the basis of the observed degree of intoxication using the intoxication-dose relationship conceived by Majchrowicz (1975). Six successive stages of intoxication were defined: neutrality, sedation, ataxia 1, 2 and 3, loss of righting reflex. Alcohol doses, ranging from 0 to 5 g/kg, were inversely related to the degree of intoxication. Assessment of the degree of intoxication and of the alcohol dose was decided by operators trained for the same evaluation criteria.

Rats were weighed once a day (at 9:00 hr). During chronic alcohol treatment, rats spent most of the time in a severe state of intoxication, unable to eat by themselves. Therefore, the loss in body weight was partially compensated by the daily oral administration (at 9:00 hr) of 20 g/kg liquid diet (Isomil, M&R, Zwolle, The

Netherlands).

Withdrawal assessment

Intensity of alcohol withdrawal signs was evaluated in each rat scoring a) spontaneous behaviour in its home cage for 10 sec, and then b) response to handling. Eleven separate items were scored using a 4-point scale (0 to 3, paralleling increased frequency of occurrence and degree of severity of items), modified from a scale described by Lal et al. (1988). The following items were rated: general activity, shakes, jerks, general tremors, head tremors, tail tremors, rigidity of muscle tone, tail rigidity, bracing posture, vocalization and spontaneous convulsions. The sum of the 11 values was the total score assigned to each rat on each observation. Scores of 8 to 9 indicated a neutrality state, corresponding to healthy and undrugged rats. Observation and scoring were carried out on a blind basis. Between observations, rats were left undisturbed in their home cage.

Experimental design

Observations and scoring were carried out every hour for 11 consecutive hours starting at 15-hr after the last alcohol administration. Prior to beginning the observation and scoring, rats were randomly assigned to 4 groups of n=8 subjects each. Animals which convulsed prior to drug administration were excluded from the study. Baclofen [(±)-baclofen; Sigma Chemical Co., St. Louis, MO, USA] was dissolved in saline (added with a few drops of a 0.1N HCl solution) and injected ip at the doses of 0, 10, 20 and 40 mg/kg (injection volume: 10 ml/kg) immediately after the 15-hr observation period.

Two separate groups of rats received 0 (n=8) and 20 (n=9) mg/kg baclofen, dissolved and injected as described above, 16 hours after the last alcohol administration. One

hour later, these rats were tested for susceptibility to audiogenic seizures, being placed in a cylindrical box of 60 cm diameter and exposed to 30-sec key shaking.

Statistical analyses

Statistical evaluation of the daily amount of alcohol administered and the loss of rat body weight in each rat group was performed by one-way ANOVAs in the study testing the effect of baclofen on the intensity of alcohol withdrawal signs, and Mann-Whitney tests in the study testing the effect of baclofen on susceptibility to audiogenic seizures. Data concerning the effects of baclofen on the intensity of alcohol withdrawal signs were analyzed by a two-way (baclofen dose X time interval) ANOVA with repeated measures on time intervals, followed by the Newman-Keuls test in order to test group differences. Occurrence of audiogenic seizures was evaluated by means of Fisher's Exact test for a 2X2 Table [treatment (vehicle, baclofen) X seizure (presence, absence)].

Results

Rats assigned to the various experimental groups did not differ in daily alcohol intake and loss of body weight during alcohol treatments. The average daily dose of alcohol administered was 9.7±0.3, 9.9±0.3, 9.9±0.4 and 10.1±0.4 g/kg [mean ± S.E.M.; $F(3;188)=0.2858$, $P>0.05$] in the rat groups receiving 0, 10, 20 and 40 mg/kg baclofen, respectively, in the study testing baclofen effect on the intensity of alcohol withdrawal signs, and 10.0±0.3 and 9.9±0.3 g/kg [mean ± S.E.M.; $P>0.05$ (Mann-Whitney test)] in the rat group receiving 0 and 20 mg/kg baclofen, respectively, in the study testing baclofen effect on susceptibility to audiogenic seizures. The average percentage of weight loss was 20.4±1.6, 19.0±0.7, 20.4±1.7 and 18.8±1.1 [mean ± S.E.M.; $F(3;28)=0.4376$, $P>0.05$] in the

rat groups receiving 0, 10, 20 and 40 mg/kg baclofen, respectively, in the study testing baclofen effect on the intensity of alcohol withdrawal signs, and 20.0±1.2 and 19.5±1.3 [mean ± S.E.M.; P>0.05 (Mann-Whitney test)] in the rat group receiving 0 and 20 mg/kg baclofen, respectively, in the study testing baclofen effect on susceptibility to audiogenic seizures.

Baclofen administration resulted in a dose-dependent, significant reduction of the intensity of alcohol withdrawal signs in alcohol-dependent rats [$F_{dose}(4;350)=8.04$, $P<0.0005$] (Fig. 1). The *post-hoc* test indicated that reduction of alcohol withdrawal score lasted for 2, 6 and 7 hrs after drug administration in the rat groups treated with 10, 20 and 40 mg/kg baclofen, respectively. The highest dose tested (40 mg/kg) induced a marked degree of muscle relaxation and sedation, as shown by a withdrawal score lower than that obtained for healthy and undrugged rats. In contrast, at the dose of 20 mg/kg baclofen, no profound muscle flaccidity and loss of vigilance were observed, and the withdrawal score approached the neutrality-state set for 4-5 hours.

A dose of 20 mg/kg baclofen significantly ($P<0.05$, Fisher's Exact test) protected rats against audiogenic seizures. Indeed, 8 out of 8 rats in the vehicle-treated group and 5 out of 9 rats in the baclofen-treated group exhibited seizures after exposure to *key shaking*.

Example 2: Effect of baclofen on voluntary alcohol intake

Animals

Male sP rats, from the 42nd generation and approximately 6 months old, were used. Rat body weight ranged between 450 and 600 g. Rats were individually housed in standard plastic cages with wood chip bedding. The

animal facility was under a reverse, artificial 12/12 hr light-dark cycle (light on at 21:00 hr), at a constant temperature of 22±2°C and relative humidity of 60%. Food pellets (MIL Morini, San Polo d'Enza, RE, Italy) were always available.

Alcohol drinking procedure

Alcohol (10% v/v, in tap water) and tap water were offered under the two-bottle free choice regimen with unlimited access 24 hr/day. Bottles were refilled every day with fresh solution and their position interchanged at random to avoid development of position preference. Alcohol and water intakes were recorded daily, immediately before lights off. All rats used in the present study fulfilled the selection criteria adopted in this laboratory to qualify as sP rats (Colombo, 1997). Rats were habituated to handling, ip injection and frequent removal of bottles.

Rats were divided into 4 groups (n=7) matched for alcohol and water intakes over the 3 days preceding the start of drug treatment. Baclofen [(±)-baclofen; Sigma Chemical Co., St. Louis, MO, USA] was dissolved in 4 ml/kg saline and injected ip at the doses of 0, 2.5, 5 and 10 mg/kg once a day (20 to 30 min prior to light off) for 14 consecutive days. Alcohol, water and food intakes were monitored daily at 8:00-9:00 hr.

Data Analyses

Data on baclofen effect on alcohol intake (expressed in g/kg), water intake (ml/kg), total fluid intake (ml/kg), food intake (g/kg) and preference ratio (percentage of alcohol solution consumed over total fluid intake) were analyzed by two-way (baclofen dose X days of treatment) ANOVAs with repeated measures on "treatment days". When appropriate, ANOVAs were followed by the Newman-Keuls test for post-hoc comparisons.

Results

The repeated daily administration of baclofen induced a dose-dependent reduction of voluntary alcohol intake in sP rats [$F_{dose}(3;312)=6.20$, $P<0.005$] (Fig. 2, panel A). The magnitude of the reduction, compared to saline-treated rats and calculated over the entire treatment period, averaged approximately 10, 20 and 30% in the 2.5, 5 and 10 mg/kg baclofen-dosed rats. A dose-dependent, significant increase in water intake in baclofen-treated rat groups [$F_{dose}(3;312)=5.12$, $P<0.01$] (Fig. 2, panel B) compensated the reduction in alcohol consumption and left total fluid intake virtually unchanged [$F_{dose}(3;312)=1.30$, $P>0.05$] (Fig. 2, panel C). The preference ratio between alcohol solution and water consumed in baclofen-treated groups reflected the changes monitored in alcohol and water consumption [$F_{dose}(3;312)=6.13$, $P<0.005$] (data not shown). Finally, ANOVA revealed a significant effect of baclofen also on food intake [$F_{dose}(3;312)=4.91$, $P<0.01$]; however, as shown in Fig. 2, panel D, the reducing effect of baclofen was limited to the highest dose tested and to the first half of the treatment period. When baclofen administration was discontinued, both alcohol and water intakes returned immediately to control levels (Fig. 2).

Example 3: clinical tests

A total of 10 male patients of mean age: 44.0±10.1 yrs with current alcoholism according to DSM IV criteria by American Psychiatric Association (1944) were studied. Baclofen was orally administered for 4 weeks, at the dose of 15 mg/day refracted in 3 times/day for the first 3 days, increasing the dose to 30 mg/day refracted in 3 times/day for the remaining 27 days.

The effects of the treatment were evaluated by the Alcohol Craving Scale (ACS) at the start of the study (T0)

and subsequently on a weekly basis until completion of treatment. (T1 – T4). ACS is a questionnaire containing 11 items, each of which requires a yes or no answer, corresponding to 1 or 0 points, respectively, and 3 multiple choice questions, to which a score of 1 is attributed for affirmative answers; the maximum craving score was therefore 14 (Gallimberti et al, 1992; Addolorato et al, 1998b). Moreover abstinence from alcohol was evaluated on the basis of the patient's self-evaluation and of family member interview, and determination of blood alcohol concentration and of alcohol in saliva by QED (Enzymatics Inc., Horsham, UK) at each outpatient control, and on the basis of the main biological markers of alcohol abuse (aspartate aminotransferase-AST-, alanine aminotransferase-ALT-, gamma glutamyltranspeptidase-GGT-, mean cellular volume-MCV-) performed at the start and at the end of the study. Finally a self-reported alcohol intake was recorded as the mean number of standard drinks consumed per day (one standard drink = 12 grams of absolute alcohol) (Secretary of Health and Human Services, 1997).

Results

Of the ten individuals recruited, one dropped out and was therefore excluded from the statistical analysis. Of the nine who completed the study, two continued to drink alcohol, although they substantially reduced their daily drinks from the first week of treatment (namely, the median value of their daily drinks was reduced from 8, as recorded prior to the start of the treatment, to 2, and then remained stable throughout the experimental period. Remarkably, the other seven subjects achieved and maintained a complete abstinence throughout the experimental period.

Baclofen was revealed as being effective in reducing

alcohol craving from the first week of drug administration (ACS median score and [range]: T0: 9 [3-14] vs. T1: 3 [0-8]; $p<0.01$); subsequently the ACS median value was stable at the different times of observation (table).

No notable difference in ACS median score was found between the abstinent patients and subjects who continued to drink at any time evaluated (table).

The most common sensation reported by patients was the disappearance of obsessive thinking about alcohol after a few days of baclofen administration. Obsessive thinking refers to a mental state in which alcoholic patients, especially in the first stage of treatment, have a constant internal dialogue about whether to use alcohol or to resist. One of these patients had experienced GHB anti-craving effects several years previously, but reported no change in his obsessive thoughts about alcohol with GHB therapy.

Comparison of laboratory data obtained both prior to and following baclofen administration, a significant decrease in values of GGT (T0: 71.7±44.2 U/l vs T4: 31.2±18.0 U/l, $p<0.01$), of AST (T0: 54.7±13.4 U/l vs T4: 23.5±10.0 U/l, $p<0.01$), ALT (T0: 55.1±17.4 U/l vs T4: 21.7±10.2 U/l, $p<0.01$) and MCV (T0: 96.3±3.4 $\mu\mu^2$ vs T4: 93.6±2.4 $\mu\mu^2$, $p<0.01$) was found.

As far as side-effects are concerned, no serious systemic or single-organ events leading to drug cessation were reported and no patients discontinued the drug. In one patient the daily dose of the drug was reduced to 15 mg per day from the 2nd week of treatment due to headache, difficulty in concentrating, lack of appetite and sedation. Tolerability was fair in all patients. No patients referred euphoria or other pleasant effects caused by the drug. No subjects showed craving for the drug; at drug

discontinuation, no drug withdrawal syndrome or side effects due to drug suspension was observed.

Table

Patients	No	T0	T1	T2	T3	T4
Whole group	9	9 (3-14)	3 (0-6)*	1 (0-6)*	1 (0-4)*	0 (0-4)*
Group A	7	8 (3-14)	3 (0-8)*	1 (0-6)*	1 (0-4)*	0 (0-4)*
Subject 1		9	2	3	2	2
Subject 2		14	8	6	4	4

Group A: abstinent subjects during the experiment period; Subjects 1 and 2: non abstinent subjects during the experiment period; * $p<0,01$ vs T0.

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Gallimberti L, et al. (1992), Alcohol Clin Exp Res 16:673-676.

CLAIMS

1. The use of baclofen or any stereoisomer thereof for the preparation of a medicament for the treatment of alcoholism in humans.

2. Pharmaceutical compositions for the treatment of alcohol addiction and withdrawal syndrome containing baclofen or any stereoisomer thereof as the active principle.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

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(54) Title: THE USE OF BACLOFEN IN THE TREATMENT OF ALCOHOL WITHDRAWAL SYNDROME AND TO PROMOTE ALCOHOL ABSTINENCE IN ALCOHOLICS

(57) Abstract: The use of baclofen for the treatment of alcohol withdrawal syndrome and promotion of abstinence in alcoholics.

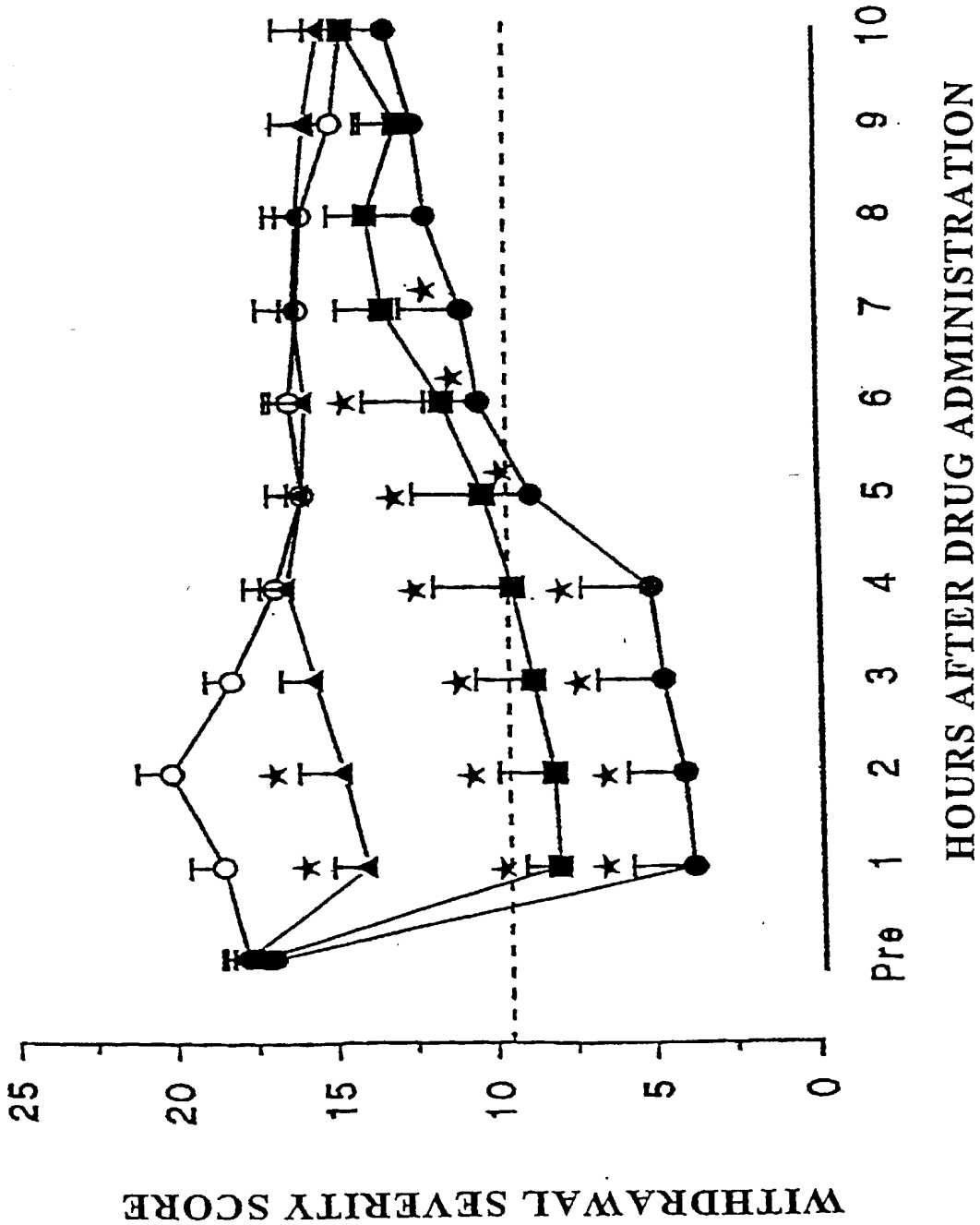
WITHDRAWAL SEVERITY SCORE
25
20
15
10
5
0
Pre
1
2
3
4
5
6
7
8
9
10
HOURS AFTER DRUG ADMINISTRATION

FIG. 1

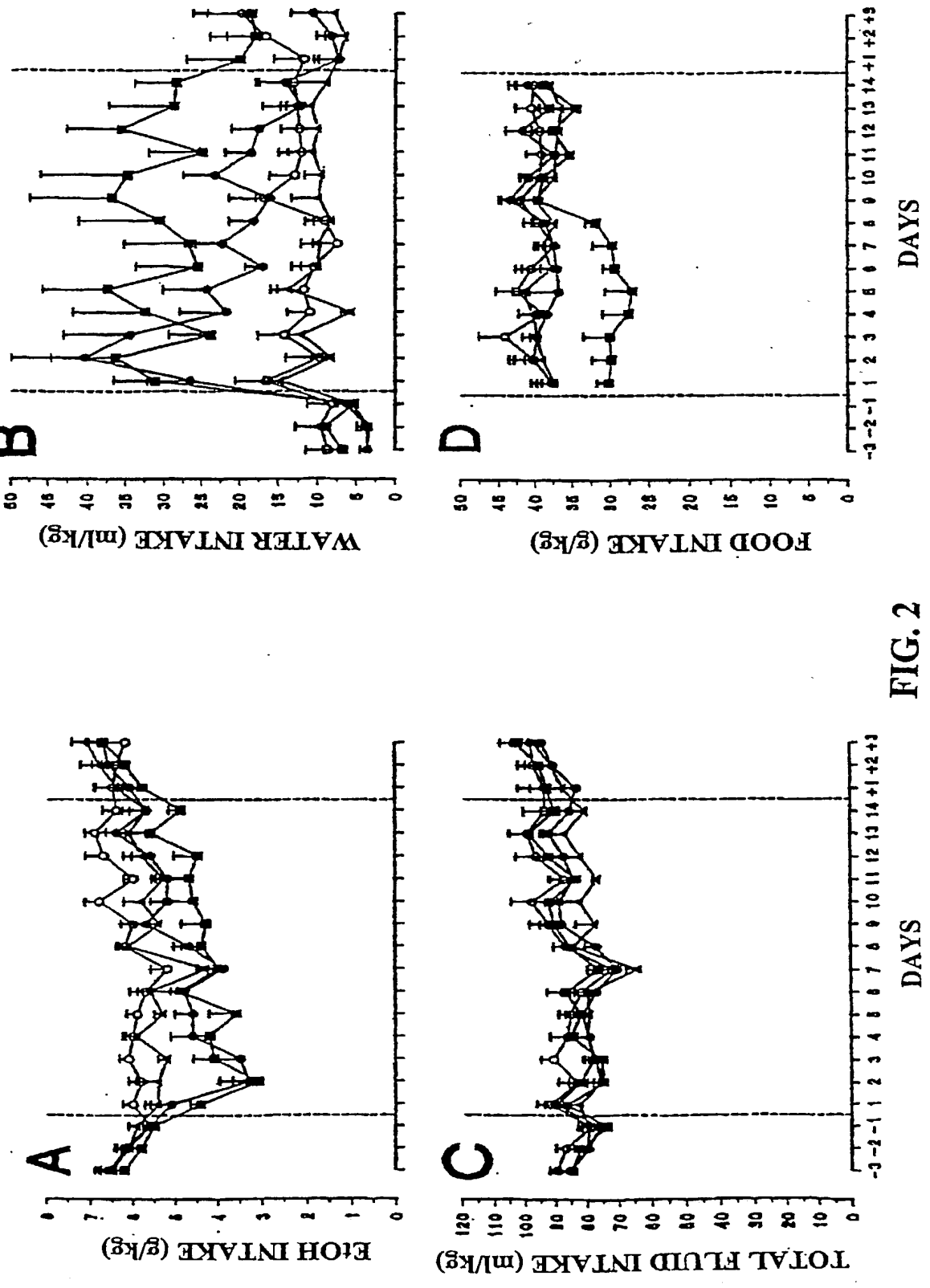
A
ETOH INTAKE (g/kg)
B
WATER INTAKE (ml/kg)
C
TOTAL FLUID INTAKE (ml/kg)
D
FOOD INTAKE (g/kg)
DAYS
DAYS

FIG. 2

10083725 .092386 ✓

Ref. _____

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

The use of Baclofen in the treatment of alcoholism

the specification of which: *(check one)*

REGULAR OR DESIGN APPLICATION

[ ] is attached hereto.

[ ] was filed on _____ as application Serial No. _____ and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

[X] was described and claimed in International application No. PCT/EP00/09750 filed on 05.10.2000 and as amended on _____ (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

PRIORITY CLAIM

I hereby claim foreign priority benefits under 35 USC 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Country	Application Number	Date of Filing (day, month, year)	Priority Claimed
Italy	MI99A002107	08.10.1999	YES

(Complete this part only if this is a continuing application.)

I hereby claim the benefit under 35 USC 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

(Application Serial No.) (Filing Date) (Status--patented, pending, abandoned)

POWER OF ATTORNEY

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from ____ _____ as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

As a named inventor, I hereby appoint the following attorney(s) to prosecute this application and transact all business in the Patent and Trademark Office connected therewith: **Robert J. PATCH, Reg. No. 17,355, Andrew J. PATCH, Reg. No. 32,925, Robert F. HARGEST, Reg. No. 25,590, Benoît CASTEL, Reg. No. 35,041, Eric JENSEN, Reg. No. 37,855, and Thomas W. PERKINS, Reg. No. 33,027**, c/o YOUNG & THOMPSON, Second Floor, 745 South 23rd Street, Arlington, Virginia 22202.

Address all telephone calls to Young & Thompson at 703/521-2297.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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